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REVIEW

Update in the diagnosis and management of preschool wheezing disorders

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ABSTRACT

Recurrent episodes of wheezing in children aged under 6 years are common and preschool children account for the majority of all childhood hospitalizations for acute wheezing. This results in significant morbidity, has an impact on the child and family's quality of life and places a significant demand on healthcare resources. Moreover, frequent preschool wheeze attacks are associated with an early loss in lung function which may track to adulthood. The focus of this review is to provide a structured approach to diagnosis and management of recurrent preschool wheezing, to prevent frequent attacks and minimize disease burden.

A detailed history and examination are critical to confirm wheezing as the predominant symptom, and to ensure alternative symptoms such as stridor, or chronic wet cough which may result from alternative diagnoses have been excluded. The constellation of wheezing with breathlessness, difficulty breathing and/or cough, supports a diagnosis of recurrent preschool wheeze. However, it is important to undertake some investigations to define the type of wheezing a child has and help decide optimal management.

In contrast to school-age asthma, preschool children with recurrent wheezing may not have an allergic, eosinophilic phenotype which will respond to maintenance inhaled corticosteroids (ICS). Assessment for aeroallergen sensitization and elevated blood eosinophils (>300 cells/mcl) when the child is well and in between episodes, helps to identify children more likely to improve with daily ICS. If neither of these tests are positive, ICS may be less effective, and assessments for lower airway bacterial infection may be helpful to decide whether treatment with targeted antibiotics is beneficial. There is preliminary evidence that oral or sublingual mixed bacterial lysates may also reduce symptoms and attacks in non-sensitized children, especially those who only have symptoms precipitated by upper respiratory infections. Recurrent preschool wheeze is heterogeneous, and management to prevent attacks should be tailored for each child. We have biomarkers to identify children who are most likely to have steroid responsive wheezing. However, evidence-based biomarkers and treatments for children with non-allergic, non-eosinophilic recurrent wheezing remain a significant unmet need.

IMPACT STATEMENT: Following the recent publication of a European Respiratory Society research statement, this review provides an update and overview of the approach to diagnosing and managing recurrent preschool wheezing. The increasing importance of using biomarkers to help guide treatments and to achieve a personalized therapeutic approach, together with current gaps in knowledge are explored.

KEY WORDS

Preschool; asthma; biomarkers; wheeze; management.

INTRODUCTION

Preschool children account for most childhood hospitalizations for acute wheeze exacerbations. Although up to 50% of children may have one episode of wheezing by their 6th birthday, only approximately 30% of those will go on to have recurrent episodes of wheezing. Recurrent symptoms, frequent exacerbations and hospital admissions in preschoolers account for one-third of healthcare costs for childhood asthma. Recurrent wheeze attacks and poor symptom control, if not effectively treated, may contribute to lower lung function trajectory to adulthood (1) and increased mortality and morbidity later in life from both respiratory and cardiovascular conditions (2).

Given the significant morbidity that results from recurrent preschool wheezing, we need a step-change in our approach to diagnosis and management to prevent attacks of preschool wheeze. Current treatment strategies tend to adopt a 'one size fits all' approach, which assumes all children with preschool wheeze will respond similarly to the same treatment, which is maintenance ICS. However, we have good evidence that preschool wheeze is heterogeneous, and not all children will respond to ICS. We therefore need to alter our approach and introduce tailored therapy by identifying those children most likely to respond to ICS and considering alternative treatments for children who are unlikely to respond. This review will summarize a practical approach to the diagnosis and management of preschool wheeze. The focus is on optimal management to prevent attacks, emphasizing the importance of both accurate clinical phenotyping and the need to investigations to identify objective biomarkers of likely treatment response.

DEFINITION OF PRESCHOOL WHEEZING

It is important to have a clear definition for preschool wheezing so that an accurate diagnosis can be made. A recent European Respiratory Society (ERS) Task Force has proposed three key criteria that should be included in the definition to ensure a consistent approach: 1. age-range 0-6 years, 2. objective confirmation of wheeze, 3. recurrent episodes of wheeze (more than one episode ever) (3).

This avoids confusion with bronchiolitis (which is often the first episode in the first few months of life). If the child then develops recurrent episodes of wheezing, this would be termed recurrent preschool wheezing. This definition allows the inclusion of children who are under a year old and ensures that wheezing is the main symptom, to minimize misdiagnosis.

CLINICAL PRESENTATION OF PRESCHOOL WHEEZE AND DIFFERENTIAL DIAGNOSIS

Before progressing to any treatments, it is essential that objective confirmation of wheezing is made (3). This may mean the child needs to be seen and examined when acutely unwell, with documentation of wheezing. If the child is being seen in a clinic setting, it is helpful to ask parents to record the child's breathing when they are unwell, or to show them a video of examples of wheezing (4), or a sound clip of a child with wheezing.

Once wheezing is confirmed, the next step is to be certain that any alternative diagnosis, that may also result in wheezing with other associated signs and symptoms, has been actively considered and excluded. A very careful and thorough history and examination are essential to ensure the diagnosis is correct. Clinical features from history or examination that should raise concern and suggest an alternative diagnosis are highlighted in **Tables 1** and **2**.

If, after a thorough history and examination, it is apparent that the child is having recurrent episodes of wheezing that are not explained by an alternative diagnosis, then an approach to management can be considered.

IS IT PRESCHOOL WHEEZE OR PRESCHOOL ASTHMA?

The specific diagnostic label that is used for a child aged under 6 years who is having recurrent episodes of confirmed wheezing, as either recurrent preschool wheeze or preschool asthma does not matter. The critical point is to understand and identify any treatable traits that are associated with the child's episodes. The Lancet commission, which brought together international experts in both adult and childhood airways diseases, has recommended the term 'asthma' should only be used as a descriptive label for a collection of symptoms, with no assumptions about underlying pathophysiology (5). The symptoms include wheezing, breathlessness, difficulty in breathing and/or cough. So, any patient that is having episodes that include this constellation of symptoms

***Table 1**. Unusual findings from history and examination that should alert to an alternative diagnosis.*

History	Examination
Symptoms present from birth/unexplained neonatal respiratory distress	Nasal polyps
Excessive vomiting or posseting	Stridor
Persistent wet or productive cough	Abnormal voice/cry
Family history of unusual chest disease	Failure to thrive
Failure to respond to conventional treatment with inhaled corticosteroids (400 mcg/day budesonide or equivalent)	Finger clubbing
Persistent/unremitting symptoms at all times	Abnormal chest shape or deformity/ recession when well
Parental anxiety	
Sudden onset, having previously been completely well	

***Table 2**. Differential diagnoses for recurrent preschool wheezing episodes.*

Tracheo/bronchomalacia
Developmental anomalies (vascular ring)
Cystic fibrosis/chronic suppurative lung disease
Recurrent aspiration – Gastroesophageal reflux/dysphagia and swallowing disorders
Chronic lung disease of prematurity
Foreign body
Immunodeficiency

may be labelled as ‘preschool wheeze’ or ‘preschool asthma’. However, what matters most is to then confirm the type of asthma or wheezing the child has.

The fundamental physiological abnormality seen in asthma is the presence of airflow obstruction, which is reversible after bronchodilator. This can be objectively measured in school-age children using spirometry and is now recommended as part of the diagnostic algorithm for school-age asthma in multiple international guidelines (6). However, for preschool children, assessments of lung function are a challenge, and are mainly undertaken in research settings (7). However, challenges around testing should not prevent attempts to confirm bronchodilator reversibility. The most practical way of doing this is to clinically assess a child for wheezing and respiratory distress before and after bronchodilator when they are acutely unwell. A documented clinical response helps to confirm the child has evidence of reversible airflow obstruction.

However, the presence of bronchodilator reversibility alone is not sufficient to guide management in this age group. It helps to confirm the diagnosis of recurrent preschool wheeze and shows a child will respond to bronchodilators when they are acutely unwell but does not help to decide what type of preschool wheeze is present, and whether the child may benefit from maintenance ICS to prevent future acute episodes. The most common pathological abnormality that is seen in most school-age children with asthma is airway inflammation, which is predominantly driven by type-2 immunity and characterized by eosinophilia (8). Most of the school-age asthma is allergic and therefore associated with eosinophilia. Maintenance ICSs are effective in school-age because they dampen airway eosinophilia. However, in contrast, it is very important to remember that preschool wheeze/asthma is not always allergic or associated with type-2 immunity. Approximately 40% of all recurrent preschool wheezers have evidence of aeroallergen sensitization, and airway eosinophilia, thus making them likely to be steroid responsive. However, a significant proportion of children with preschool wheeze do not have any evidence of allergic sensitization and may not have type-2 driven disease.

PRESCHOOL WHEEZE IS HETEROGENEOUS

Before making decisions about appropriate maintenance therapy to prevent attacks for children with preschool wheeze, it is important to use information from history, examination and to undertake additional investigations to define the type of preschool wheeze a child has.

It has been proposed, from expert consensus, that a child's symptom pattern may help to determine response to ICS (9). It is suggested that children who only wheeze during acute episodes precipitated by upper respiratory infections, may be less likely to respond to maintenance ICS, while those who wheeze during and between episodes will respond to ICS better. However, this includes an assumption that the phenotypes determined by symptom pattern alone will remain stable, which we know is not the case (10). It also includes an assumption that phenotype determined by symptom pattern relates to airway inflammation and pathology, which is also not true (11). This can be illustrated by the Case descriptions summarized in **Box 1** and **2** below.

As can be seen, both patients have been prescribed maintenance ICS to try to prevent recurrent episodes of wheeze, and despite this, both continue to have severe episodes requiring hospitalizations and intravenous therapy. So how can we decide which child is on the correct treatment? There are several differences between the cases that can be highlighted from history. The child in Case 1 only ever has episodes with an upper respiratory infection, she is completely well in between. She also does not have any personal history of atopy or allergic disease, but she does have a family history of atopy and asthma. In contrast, Case 2 has symptoms that are triggered by exercise and exposure to cats, in addition to when she has an upper respiratory infection, she also has eczema and food allergies. If we now define the type of preschool wheeze for each case from history, we can say:

– Case 1: non-atopic with recurrent infection (viral) induced wheeze.
– Case 2: atopic with recurrent (persistent) preschool wheeze with food allergies and eczema.

A good history has helped to define the type of wheezing the two patients have and suggests Case 1 may not have type-2, eosinophilic airways disease and Case 2 is more likely to have allergic, type-2, eosinophilic airways disease. But Case 1 does have a family history of atopy and asthma, and they both continue to have severe episodes, so how can we be more certain about the best approach to management?

Box 1. Case 1.

- 2-year-old Caucasian girl
- Recurrent episodes of breathlessness/wheezing
- Always at the onset of a cold, well in between
- 10 acute admissions since 14 months old
- Worst episode needed Optiflow and iv MgSO4
- No eczema/no food allergies
- Father: asthma, eczema, hay fever, peanut allergy
- Prescribed Beclometasone 100 mcg 2 puffs bd and prn salbutamol

Box 2. Case 2.

- 3-year-old Afro-Caribbean girl
- Recurrent wheeze episodes since first year of life triggered by viral infections
- 4 acute attacks in the last 6 months needing iv MgSO4, oxygen
- Symptoms triggered by exercise and exposure to cats
- Food allergies: egg, fish, cashews, sesame
- Eczema
- Prescribed Seretide 125/25 mcg 1 puff bd and prn salbutamol

OBJECTIVE TESTS TO HELP DEFINE THE TYPE OF PRESCHOOL WHEEZE

Although it is very likely that Case 2 above has allergic, eosinophilic preschool wheeze. It is becoming apparent that investigations are helpful, in addition to a good history, to identify children who are differential responders to maintenance ICS.

One of the first studies to demonstrate the utility of objective tests in preschool children to identify differential responders to daily ICS was the Individualized Therapy for Asthma in Toddlers, 'INFANT' study, which was a multicenter, randomized, double-blind, clinical trial in children aged 12 to 59 months with asthma, who needed daily controller therapy (12). Children had 3 crossover periods with daily ICS, daily leukotriene receptor antagonists, and as-needed ICS. The primary outcome was

differential response to medication based on a composite measure of asthma control. The findings showed that 25% of preschool wheezers showed no response to daily ICS, and the others showed a spectrum of response (12). Good response to daily ICS was demonstrated in children with either aeroallergen sensitization or blood eosinophils ≥300 cells/μL. The best response was seen in those who were positive for both biomarkers. This showed objective phenotyping with aeroallergen sensitization and blood eosinophil counts is useful for guiding treatment selection and identifies children with frequent exacerbations for whom treatment with a daily ICS is beneficial.

In the Cases above, these tests would be helpful to understand whether both patients should continue maintenance ICS.

BASICS OF ASTHMA MANAGEMENT ARE AS IMPORTANT FOR PRESCHOOL AS SCHOOL-AGE CHILDREN

The interesting point about the cases is that the child with the allergic, eosinophilic phenotype (Case 2) continued to have severe exacerbations despite being prescribed high-dose maintenance treatment. When this occurs, it is essential to remember that ensuring the basics of management have been optimized for children with preschool wheeze/asthma just as we do for school-age children with difficult-to-treat asthma (13). If the phenotype is confirmed as being steroid responsive, then the next step should not be automatic therapy escalation, but should include assessment of inhaler technique, parent/caregiver education to ensure they understand the prescription and why the ICS administration is important and obtaining evidence of adherence to the ICS. Simply relying on parental reports about adherence is not sufficient, as up to 50% of wheezers, even those with severe disease, have been shown to have sub-optimal adherence when assessed using electronic monitors (14). In Case 2, when the basics were checked, it became apparent that the child was not receiving the ICS regularly, and this was the main explanation for the repeated and severe presentations.

Other factors that are critical for all preschool children with recurrent wheeze that will contribute to exacerbations and poor symptom control, include avoidance of exposure to cigarette smoke and vaping (15). In addition, for those who have allergic sensitization, avoidance of the allergens to which they are sensitized is as important in this age group as in school-age children. A latent class analysis of 5 clinical trials that investigated efficacy of ICS in preschool wheeze showed although each trial had shown benefit from ICS compared to placebo in all children as a group, in research setting of high adherences, daily ICS did not affect exacerbations rates compared to placebo in children with minimal sensitization and those with tobacco smoke exposure (16).

MANAGEMENT OF PRESCHOOL WHEEZE IN NON-ALLERGIC CHILDREN WITHOUT PERIPHERAL EOSINOPHILIA

Although we know how to identify children who are most likely to respond to daily ICS treatment, the biggest remaining challenge is how we should manage preschool children with recurrent wheezing who do not have allergic sensitization or evidence of elevated blood eosinophils. It is becoming increasingly apparent that for some children with recurrent wheezing, lower airway infection may be the main cause of their symptoms. Unbiased analysis of lower airway inflammation in children aged 1-16 years with severe wheezing and asthma has shown two distinct lower airway inflammation clusters in children under 5 years. A cluster with predominant allergic sensitization which was steroid responsive and a second cluster that was predominantly neutrophilic and steroid refractory (17). In a further study which assessed lower airway inflammation and infection in recurrent severe wheeze, four clusters were identified, an atopic cluster with associated blood eosinophilia, a non-atopic cluster with low infection rate and high use of ICS, a non-atopic cluster with high rates of both bacterial and viral infection with an associated lower airway neutrophilia and a non-atopic cluster with low infection rate and no use of ICSs (11). This suggests a sub-group of recurrent wheezers, who are non-atopic, have lower airway bacterial infection that may respond to targeted antibiotics. A further cluster analysis of preschool wheezers who had “treatment-refractory” symptoms, not responsive to ICS, has shown 4 clusters: airway malacia, gastroesophageal reflux, lower airway rhinovirus predominant, and type-2high inflammation (18).

Evidence for both viral and bacterial infection and neutrophils playing a role in recurrent wheezing is becom-

ing increasingly apparent. Very consistently, three bacteria are most commonly cultured from the lower airways of preschool wheezers. These are *Hemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis* (11,19). Importantly, the bacteria are identified when children are clinically stable and well, suggesting the picture of persistent bacterial bronchitis which may precipitate acute attacks upon acute exposure to viruses or allergens. An observational study of severe, recurrent wheeze has shown prolonged treatment with targeted antibiotics for between 2-16 weeks in preschool children who had lower airway bacterial infection resulted in fewer episodes of dyspnea and fewer hospitalizations in the subsequent year (19). Therefore, in children without allergic sensitization, or blood eosinophilia, bacterial infection may be an important factor that contributes to recurrent wheeze, however, clinical trials of efficacy are currently lacking.

Another approach that has shown promise, specifically for preschool children with infection induced wheezing and no allergic sensitization, is the use of mixed bacterial lysates. These are orally or sublingually administered lysates of mixed respiratory pathogenic bacteria which have, to date, been used in many parts of Europe and Southeast Asia to prevent recurrent respiratory tract infections (20). Although we are unaware of the precise mechanism of action of the bacterial lysate compounds, it has been proposed from animal studies that there may be two mechanisms of action. The first is a skewing of early-life immune responses away from predominantly type-2 responses, towards stronger type1 responses, needed to fight infections. The second is the concept of trained immunity (21, 22). Numerous meta-analyses have been undertaken to understand their efficacy for the prevention of both respiratory tract infections and wheeze episodes in young children, however, the data remain conflicting, and currently no strong recommendations can be made from the existing literature, because of the high heterogeneity randomized trials and systematic reviews (23). A recently randomized, placebo-controlled trial including 120 children aged less than 3 years, with at least 3 wheezing episodes in the previous year, in which children with aeroallergen sensitization were excluded, assessed the efficacy of sublingual mixed bacterial lysates given for 6 months on the primary outcome of wheeze exacerbations at 1 year (24). There were significantly fewer exacerbations, fewer symptoms and better medication scores for 1 year in the children who received the mixed bacterial lysates. This provides very encouraging evidence that an intervention, given for non-allergic preschool wheezing has shown benefit not just for the duration of the treatment, but a sustained benefit up to 6 months after the treatment was stopped. This is even more encouraging than the data we have for ICS, in terms of sustained efficacy of an intervention after treatment has stopped, and potential for preventing progression of disease. Although 6 months after the intervention is a relatively short period, especially because of the potential influence of a seasonal effect in these children, where the Spring and Summer months are often a period of 'natural resolution' this does show encouraging results.

There are several clinical trials that are currently ongoing to confirm these preliminary findings of efficacy of bacterial lysates for non-allergic preschool wheeze. The Oral Bacterial Extract for the prevention of Wheezing Lower Respiratory Tract Illnesses (ORBEX) trial is currently ongoing. This is a randomized trial investigating the impact of an oral mixed bacterial lysate compound, Bronchovaxom®, on the prevention of wheezing lower respiratory illnesses. Children aged 5-17 months, with at least 1 parent with asthma, or the child with eczema, were randomized to receive Bronchovaxom® or placebo for 2 years, and the primary outcome to be assessed is wheezing 3 years later. Robust clinical evidence is needed before recommendations can be made for either the use of bacterial lysates or antibiotics to prevent attacks of preschool wheeze in non-allergic children who do not have blood eosinophilia and are unlikely to respond to ICS.

SUMMARY

Recurrent wheezing episodes in preschool children are among the most common reasons for unscheduled healthcare attendance and hospitalizations globally. Moreover, longitudinal studies show children with frequent and severe attacks are at risk of developing low lung function by school-age, which tracks a low trajectory to adulthood. The need to reduce acute episodes and disease burden is an urgent priority that requires effective interventions. After confirming recurrent wheeze objectively, and excluding alternative diagnoses, it is important to look for objective markers of response to ICS, such

as aeroallergen sensitization and blood eosinophils. The current gap in knowledge centers is specifically for children who do not have a pathological phenotype that is steroid responsive. We have increasing evidence of potential therapies that can be used, but robust clinical trial evidence for the efficacy of antibiotics and bacterial lysates in children who do not have the steroid-responsive phenotype is needed. It is critical to ensure interventional studies are designed using precision medicine, such that treatments are targeted at the individual child's risk factors and disease pathophysiology. This means we need to consider innovative trial designs and analysis approaches that can be used to understand the efficacy of interventions in relatively small populations.

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Author declares no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

Data falsification and fabrication

All the data corresponds to the real.

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